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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,879	04/25/2006	Bent Karsten Jakobsen	007547.00001	9328

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,879	JAKOBSEN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,55-59 and 86-89* is/are pending in the application.

4a) Of the above claim(s) *55-59,88 and 89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,86 and 87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/1/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/09 has been entered.

Status of the Claims

Claims 1, 6, 55-59 and 86-89 are pending in the instant application.

Claims 55-59 and 88-89 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. [Note that claims 88-89 are drawn to a modified or mutant form of a TCR bound phage. However, claim 1 does not recite a mutant or a modified form of said TCR. Accordingly, the claims to a mutant (i.e., by substitution) have been withdrawn from consideration.]

Claims 1, 6 and 86-87 are under examination.

Withdrawn Rejections

In view of the amendments to the claims and applicants' arguments, the rejections under 35 USC 112, second paragraph and 35 USC 103 over Boulter are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The disclosure is objected to because of the following informalities: page 67, for example, X is not defined for the sequences that contained said X.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1, 6, 86-87, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to describe a composition of the polypeptide comprising first and second polypeptides as claimed. The specification at page 17, lines 8-20 only mentions in general terms first and second polypeptides. A skilled artisan

cannot readily ascertain whether the first and second polypeptides flanking the TCR, if this is the intent of the claimed scope, are the same or different or if the entire first and second polypeptides consist only of dimeric TCR. The claimed first and second polypeptides would encompass numerous residues individually or in combinations, not to mention the length, encompassed by said huge first and second polypeptides. Applicants therefore at the time of filing are not in possession of the huge scope of the first and second polypeptides linked by disulfide in any portion of any constant region of a TCR molecule. As applicants state at pages 8 and 9 of the instant REMARKS:

The phenomenon of poor pairing efficiency of TCR chains was widely recognized. For example, see Chang et al.....and Pecorari et al:

• Chang, Abstract: "Generation of soluble T-cell receptor (TCR) molecules by a variety of genetic engineering methods has been hampered by inefficient pairing of α and β subunits in the absence of their respective transmembrane regions and associated CD3 components."

• Chang, page 11410, col. 2, paragraph commencing at line 3: Just before the sequence it is said "the majority of α and β

proteins are present as monomers... and thus do not associate with each other."

• Pecorari, page 1832, col. 1, bottom of page: "However, attempts to refold TCRs in vitro or to express them functionally, whatever their sequences or formats, encountered great difficulties in many laboratories."

• Pecorari, page 1832, col. 2, under "General Considerations": "Preliminary experiments with refolding a series of TCR constructs of different T-cell clones.. have led us to the conclusion that no published method or format of the recombinant TCR... appeared to be of general utility. Great differences between the aggregation tendencies of different TCRs became apparent."

• Pecorari, page 1836, col. 2, line 21 from bottom: "Considering the large interaction surface between Vα and Vβ and Cα and Cβ, this dissociation constant is quite high, especially when compared with the corresponding KD observed for heavy and light chains in Fab fragments .... "

• Pecorari, page 1836, col. 2, line 8 from bottom: "this weak affinity between the α and β chains may be related to the more polar constant domain interface in the TCRs compared with the more hydrophobic one in antibodies."

Response to Arguments

Applicants state that claim 1 is amended to recite that the first and second polypeptides consist essentially of the recited components.

In reply, the amendment adding the phrase "consist essentially of" does not obviate the rejection. More importantly, the as-filed specification does not describe with said phrase the residue(s) that can be modified such that the polypeptide's folding is achieved (see applicants' REMARKS above). The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). Herein, the claims do not recite for any TCR structure. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the

invention."). See also AK Steel Corp. v. Sollac, 344 F.3d 1234, 1240-41, 68 USPQ2d 1280, 1283-84 (Fed. Cir. 2003). If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention (absent any particular structure of TCR, as claimed). In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See MPEP 2111.03 [R-3].

Claim Rejections - 35 USC § 112, second paragraph

Claims 1, 6, 86-87, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 6 is indefinite as to recitation of "wherein the C-terminus of one member of the dTCR is linked by a peptide bond to a surface exposed residue of the phage particle" as the C-terminus of each of the polypeptide are each linked to the N-terminus of the other polypeptide. Also, the inconsistent use of terminologies "member" and first or second polypeptide provide for confusion and ambiguity.

2. Claim 6 recites the limitation "surface exposed residue of the phage particle". There is insufficient antecedent basis

for this limitation in the base claim. Also, it is not clear as to the means or manner of said surface exposed residue. For example, what is the depth, the length and kind of residue(s) exposed on the phage particle?

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1, 6, 86-87, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Weidanz [(J. Immunol. Methods)(I) or (WO 99/18129) (II)] in view of Jakobsen et al (US 2002/0142389) and Reiter et al.

Weidanz (I) discloses at e.g., page 59, the abstract, a bacteriophage display on its surface a heterodimer, single chain T-cell receptor(scTCR) comprising of a polypeptide, variable α(V α) and polypeptide variable β(Vβ) and a constant region C β. See further page 60, col. 1 and col. 2 and page 73, col. 1.

Claim 6 linking of TCR at the C-terminus to the N-end of phage is disclosed at page 73, col. 2.

Weidanz (II), throughout the patent, basically discloses the same dimer TCR as disclosed at e.g., the abstract. Each of Weidanz (I or II) does not disclose that the disulfide bond interchain is at residues of constant domain sequences. However, Li discloses at e.g., pages 528-529

under the DISCUSSSION heading that the C domain of TCRβ is responsible for binding to the TCRα chain. The interchain bond as taught by Li may play an important role in stabilizing the molecular structure so that a functional TCR complex can occur.

Jakobsen et al discloses at e.g., paragraph [0064] that the constant domains are not directly involved in contacts with the peptide-MHC ligands, the C-terminal truncation point may be altered substantially without loss of functionality. The advantage of fusing heterodimerisation domains just prior to the position of the cysteines forming the interchain disulphide bond is that the α and β chains are held in close proximity in the cellular receptor. Therefore, fusion at this point is less likely to impose distortion on the TCR structure. Jakobsen discloses at e.g., paragraph [0066] that in addition to aiding interchain stability through a heterodimerisation domain, the incorporation of cysteine residues which could form an interchain disulphide bond could be used. If shorter fragments of the α and β chains were expressed, cysteine residues could be engineered in as substitutions at amino acid positions where the folding of the two chains would bring the residues in close proximity, suitable for disulphide bond formation.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to link the constant region of the TCR in the phage particle of Weidanz(I or II). As applicants state Weidanz suggests modifying the parent TCR to obtain the binding fragment scTCR. This is an implicit teaching that the art has recognized the successful fusion of the parent and the overriding question was whether its fragment could similarly be fused. Following the success in fusing antibody which is similar in structure with TCR(see Reiter and the instant specification at e.g., page 1, lines 19-20, page 3, line 20 up to page 5,line 30) one would have a reasonable expectation of success in fusing either the parent or fragment of TCR to a phage particle. Li or Jakobsen teaches the numerous advantages in linking the constant region of the TCR molecule such as stabilizing the TCR molecule. Additionally, Jakobsen teaches that the constant region is not involved in direct contact with antigen. Thus, at the time of applicants' invention fusion of either the TCR parent structure or its (binding) fragments into a phage would be within the realm of one having ordinary skill in the art.

Response to Arguments

Applicants assert that the Abstract of Weidanz (I) mentions only single chain TCR phage display.

In reply, in considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also **inferences** which one skilled in the art would reasonably be expected to draw therefrom. In re Preda 159 USPQ 342.(Emphasis added).

Applicants assert that Weidanz at page 60, col. 1 does not disclose phage display of dimeric TCRs. In fact, the paragraph at the bottom of page 60, col. 1 states:

> In contrast to the success of phage-display systems for Abs (i.e. antibodies) display of alpha/beta TCR molecules on the surface of phage has not been successfully achieved.... The lack of success is the result of technical problems associated with the expression of soluble TCR in E. coli....

Weidanz I therefore confirms what has been said above in the discussion of Chang and Percorari.

In reply, applicants have taken out of context the teachings of Weidanz, The complete citation at the bottom of page 60, col. 1 states:

> In contrast to the success of phage-display systems for Abs (i.e., antibodies) display of alpha/beta TCR molecules on the surface of phage has not been successfully achieved **.... The lack of success is the result of technical problems associated with the expression of soluble TCR in**

> **E. coli .... To address these technical difficulties with phage display of TCR, we selected the murine TCR....**We chose this TCR because it's ligand ...is known…In addition, to show the generality of TCR phage display, we expressed a different TCR specific for peptide fragment ….The development of TCR phage-display technology… would be expected to have many applications besides isolating TCRs with unique specificity from TCR phage-display libraries….(Emphasis added).

Applicants state that the mention of DO 11.10 as a heterodimeric TCR is simply a reference to the parental TCR which Wiedanz is going to reform as a single chain TCR for phage display. The authors obviously did not even contemplate the phage display of the parental heterodimer, because they, like the rest of the art, believed that the weak interchain binding energy of TCRs would prevent proper display.

In reply, applicants' arguments are not commensurate in scope with the claims which do not recite parental heterodimer. Be it as it may, the fact that Wiedanz suggests the parent TCR would lead one having ordinary skill in the art to the parent molecule. This is a norm in the art i.e., after the parent test, the fragment follows. Since the parent antibody has been successfully fused to which the TCR is known to be of similar structure hence, Weidanz suggests the parent and test the fragment. Attention is drawn to Reiter at e.g., page 281 which states:

> The T cell antigen receptor (TCR) is a membrane-bound receptor composed of two chains, α and β, each consisting of an N-terminal variable region (V) and a C-terminal constant region (C)…. Analysis of the sequences of the TCR chains indicate that they have a framework closely related to that of immunoglobulins…Thus, it was proposed that the three-dimensional structure of TCR should be similar to the structure of antibodies..

Applicants assert that Weidanz II does not add anything to the disclosures of Weidanz I. The secondary reference, Reiter, does not relate to phage display. It is entirely unknown whether the Reiter construct would refold functionally in the expression bacterium if one of the variable domains were expressed fixed to the phage coat protein, and the other variable domain were expressed free.

In response, Reiter is employed not for the purpose as argued. Rather for its disclosure as to the similarity in structure of the native TCR and antibodies. Since antibodies, whether the parent or its fragments has been successfully fused to a phage particle hence, one would reasonably expect successful fusion for a similar compound as TCR.

Applicants state that the present invention requires both constant domains to be present, and positions an interchain bond between cysteines in the constant domain. By locating the interchain bond well away from the variable domains, the present invention enables the TCR to refold with the variable domain in

a completely natural functional configuration. Even if the Reiter construct were to assemble if expressed in a phage display system, the bond would be between residues in the variable domains and inevitably would induce a less than natural refold. The prior art - including the cited Weidanz and Reiter references - is silent on how to ensure successful expression of phage particles displaying functionally folded heterodimeric TCRs. The references relied on by the examiner do not contain the slightest hint that the provision of an interchain disulfide bond between constant regions would enable what had not been previously available, namely successful phage display of dimeric TCRs.

In reply, obviousness does not require absolute predictability. Applicants' arguments are not commensurate in scope with the claims. The claims do not recite expression of phage particles displaying **functionally folded** heterodimer TCRs. The claims lack any specific structure for TCR to be considered for any functional folding. Li has successfully linked the constant region, α and β, and teaches the advantage obtained in said linking. Jakobsen also teaches the use of the non-reactive constant region in binding. Thus, the combined teachings of the prior art would lead one having ordinary skill in the art to the claimed heterodimer TCR fused to phage particle.

Applicants are in effect, arguing that a structure suggested by the prior art and hence, potentially in possession of the public, is patentable to them because it also possesses an inherent, but hitherto unknown, function (or property, as folding) which they claim to have discovered. This is not the law. A patent on such a structure would remove the public that which is in the public domain by virtue of its inclusion in, or obviousness from the prior art. (In re Wiseman 201 USPQ 658).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/

Primary Examiner, Art Unit 1639